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Arsenic and Obesity: A Compound Risk Factor for Diabetes? with Mirek Stýblo

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Although obesity is a major risk factor for diabetes, certain environmental agents, such as arsenic, also appear to contribute to the disease. There is evidence that an individual's risk of arsenic-related disease depends on how efficiently he or she metabolizes arsenic. But what if that individual is both obese and exposed to arsenic? In this podcast, guest Mirek Stýblo discusses his recent work exploring the role that diet plays not just in arsenic metabolism but also in the diabetogenic effects of arsenic. https://doi.org/10.1289/EHP4885

NARRATOR: *EHP* presents "The Researcher's Perspective."

AHEARN: It's "The Researcher's Perspective." I'm Ashley Ahearn.

More than 200 million people are thought to be exposed to naturally occurring arsenic in drinking water around the world, at levels above the guideline values established by the World Health Organization.[1] Inorganic arsenic occurs in rock formations and soil and can get into water supplies and crops. It's also found at some hazardous waste sites.

Long-term exposure to inorganic arsenic has been linked to health problems like cancer and even diabetes. Our bodies can detoxify inorganic arsenic to a certain extent, but public health scientists want to better understand how that works in order to find ways to minimize the health effects of arsenic exposure for millions of people.

Dr. Mirek Stýblo is the coauthor[2] of a new paper[3] in *Environmental Health Perspectives* that explores this subject. He's a professor in the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. Dr. Stýblo, welcome to "The Researcher's Perspective."

STÝBLO: Thank you for inviting me.

AHEARN: Okay. What was the key question you were trying to answer in this study?

STÝBLO: Well, first, simply, we wanted to see if folate intake modulates arsenic metabolism and diabetogenic effects of arsenic in mice.

AHEARN: So exposure to inorganic arsenic has been linked to type 2 diabetes. Can you help me understand how that works, and what's the mechanism by which arsenic might be triggering diabetes?

STÝBLO: Well, let me just first say that, first of all, inorganic arsenic has been known as a carcinogen. And so, all the regulations we now have for arsenic in drinking water are really based on the carcinogenic effects of arsenic. However, we now have a very large body of evidence to suggest that arsenic is also a diabetogen. So, there are population studies that linked arsenic exposure from drinking water to increased diabetes risk among various populations around the world. And there are laboratory studies that use mice or *in vitro* models like cells in a dish to show that arsenic does alter glucose and insulin metabolism in a way that is consistent with diabetes.

So, this is a relatively new area in arsenic toxicology, but a very fast developing area because given the large prevalence of obesity and diabetes in this country and practically anywhere around the world—anything that could contribute to diabetes risk we want to know about, and we want to make sure we can, we can reduce that risk.

AHEARN: So, Professor, you were exploring whether or not folate might mitigate those effects, it appears. Could you tell me a little bit more about how you conducted your study using mice in the lab?

STÝBLO: What we did in this study, we used two types of mice. One type was just a regular mouse strain[4] that is very frequently used in obesity and diabetes research in lab settings. And the other mouse strain used[5], these mice lacked a gene that metabolizes arsenic. So, these mice were not able, or are not able, to detoxify arsenic in any efficient way. And using these two mice, we exposed them to either pure, arsenic-free water or water in which arsenic was added to a relatively low level, a hundred micrograms per liter.

But we also fed them two types of diet. So first we started with a low-fat diet that is purified, meaning there are perfectly defined amounts of perfectly known chemical compounds, nutrients. The other type of diet we used, after 24 weeks of feeding this low-fat diet, was a high-fat diet, also purified. And this diet is generally used in laboratory settings to produce obesity and to study obesity-associated diabetes. So that was the basic design.

And while feeding these two types of diets and exposing mice and having control mice drinking pure water, we were measuring indicators of diabetes. Same thing you would do in human studies, so, fasting blood glucose and fasting insulin levels in blood. You also look at body composition, and that is a specific instrument that can measure percentage of fat in the body—in other words, measuring how mice are getting obese or not. And this together, along with some measures of arsenic metabolism and folate, allow us in the end to analyze the association between these different conditions and the diabetogenic effects, or in other words, the diabetes as an outcome.

AHEARN: Okay, so you've got these two groups of mice, and they're being fed high-fat diets and normal diets, and then you introduce folate. What did you find then?

STÝBLO: So, we had two extreme levels of folate, something you probably would not be able to find in a human population. And here is an advantage of a laboratory study: You can actually design an experiment, you control a lot of important conditions. So, we use very low levels of folate in, on one side, which would constitute almost folate deficiency but still has no adverse effects in adult mice, and we used very high levels of folate as a folate supplementation, which is not necessarily natural, although some people are using so much folate that that may be basically at the level of over-supplementation. So, having these two extremes, we expected extremely profound effects on arsenic metabolism and also on the outcome; in other words, in diabetes.

AHEARN: And what did you find?

STÝBLO: Well, not exactly what we expected. So, having this very large difference in folate intake, we found relatively minor effects on arsenic metabolism. We did find similar effects that, you know, like those published in human studies. In other words, our data indicated that arsenic metabolism was stimulated by a certain margin, not a big margin. But in addition to urine, we were able to look inside of the body. We looked in the liver. So, we confirmed that what we see in urine is actually consistent with what we see in the liver, which is something you cannot do in human studies. So, there was a stimulation, but this stimulation was found only in female mice. And if you ask me why, I would have to say, well, I don't know.

So, there was an effect on metabolism in females which appeared to be stimulating arsenic metabolism, but we didn't find actually any major effect on what we call phenotype of mice while those mice were fed a low-fat diet. In other words, exposure to arsenic did not really produce any adverse effects—diabetogenic or others—and folate had really no effect on how these mice demonstrated glucose metabolism or insulin metabolism while on a low-fat diet. So that was the reason why we switched these mice to a high-fat diet.

What we basically did, we added another hit, another diabetogen. The diabetogen is obesity; obviously, most of the diabetes is associated in human populations with obesity, type 2 diabetes. So that's what we did here, and that was after we actually switched those mice on a high-fat diet and let them go for thirteen weeks. These mice obviously became obese, and that was at this point when we actually see effects of arsenic exposure. In other words, arsenic exposure did increase one of the diabetes indicators, insulin resistance. And interestingly, folate—high folate—intake prevented this increase. And interestingly, it prevented it in both males and female mice, but again it affected arsenic metabolism only in female mice.

AHEARN: Okay. So, if you are an obese mouse and you're exposed to inorganic arsenic and you also take folate, your body is better at handling the arsenic. Do I have that right?

STÝBLO: You do, and I would actually—I would probably say if you are folate deficient and you are obese and you are exposed to arsenic, then your risk of diabetes increases.

AHEARN: So what do you think folate is doing here? Do we know how it's affecting the way mice metabolize inorganic arsenic?

STÝBLO: Well, after what we see in this study, I don't actually believe that folate intake has much to do with how mice are metabolizing arsenic, because if it does, it's sex dependent. And that's actually one of the intriguing results of this study. We see this increase of arsenic methylation in females only, so the question, next question we are asking is, why is that? Why it is working only in females while human studies do not seem to see sex-specific effects of folate.

AHEARN: So tell me, Professor, what might your results suggest when it comes to type 2 diabetes risk in populations that are exposed to inorganic arsenic?

STÝBLO: Well, the other issue, and the other important observation from this study, is really interaction between obesity and arsenic. So, you have two diabetogens, right? One originally recognized, obesity, obviously is linked to diabetes, and one that is being recognized as a diabetogen right now. And playing together, these two diabetogens further increase the risk of diabetes.

And interestingly, you know several months ago, a group of researchers from Berkeley led by Craig Steinmaus published a study from Chile, from their human cohort in Chile, that came up with exactly the same finding.[6] Obese individuals exposed to arsenic were at higher risk of developing diabetes or being diagnosed with diabetes when exposed to arsenic. So again, they show exactly same outcome in a human study. Now we are able to reproduce it in my study. So, I think this is a very important observation that needs to be further explored in both laboratory settings and in human research. But folate, you know, could be good for you, but I think the big message from this study really is the interaction between obesity and low arsenic exposure.

AHEARN: Dr. Stýblo, thank you so much for joining me.

STÝBLO: Thank you for inviting me. I enjoyed it very much.

AHEARN: Dr. Mirek Stýblo is a professor in the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill. His study on the role of dietary fat folate and inorganic arsenic exposure in mice appears in the December 2018 issue of *EHP*.

I'm Ashley Ahearn. Thanks for listening to "The Researcher's Perspective."

The views and opinions expressed in this podcast are solely those of our guest and do not necessarily reflect the views, opinions, or policies of Environmental Health Perspectives *or the National Institute of Environmental Health Sciences.*

References and Notes

1. WHO (World Health Organization). 2008. Guidelines for Drinking-water Quality: Incorporating First and Second Addenda to Third Edition. Vol. 1—Recommendations. Geneva:WHO Press. Available: https://www.who.int/water_sanitation_health/publications/gdwq3rev/en/ [accessed 29 December 2018].
2. Dr. Stýblo wishes to give special thanks to his coauthors and collaborators Madelyn C. Huang and Christelle Douillet for their help and support in conducting this research.
3. Huang MC, Douillet C, Dover EN, Zhang C, Beck R, Tejan-Sie A, et al. 2018. Metabolic phenotype of wild-type and *As3mt*-knockout c57bl/6j mice exposed to inorganic arsenic: the role of dietary fat and folate intake. Environ Health Perspect 126(12):127003, https://doi.org/10.1289/EHP3951.
4. C57BL/6J wild-type mice.
5. *As3mt*-knockout mice.
6. Castriota F, Acevedo J, Ferreccio C, Smith AH, Liaw J, Smith MT, et al. 2018. Obesity and increased susceptibility to arsenic-related type 2 diabetes in Northern Chile. Environ Res 167:248–254, PMID: 30059859, https://doi.org/10.1016/j.envres.2018.07.022.